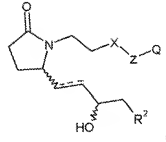
CLAIMS

What is claimed is:

1. A method of treating a condition which presents with low bone mass in a patient presenting with low bone mass, the method comprising continuously administering to the patient presenting with low bone mass a synergistically effective combination of a first compound and a second compound, the first compound being of the formula I



I

a prodrug thereof, a pharmaceutically acceptable salt of said compound or said prodrug or a stereoisomer or diastereomeric mixture of said compound, prodrug or salt, wherein:

the dotted line is a bond or no bond;

X is $-CH_2-$ or O;

Z is $-(CH_2)_{3-}$, thienyl, thiazolyl or phenyl, provided that when X is O, then Z is phenyl;

Q is carboxyl, (C_1-C_4)alkoxylcarbonyl or tetrazolyl;

R^2 is -Ar or $-Ar^1-V-Ar^2$;

V is a bond, -O-, $-OCH_2-$ or $-CH_2O-$;

Ar is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring or bicyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; and

Ar^1 and Ar^2 are each independently a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms

selected independently from oxygen, sulfur and nitrogen, said partially or fully saturated ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur;

said Ar moiety is optionally substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, or on one or both rings if the moiety is bicyclic, with up to three substituents per ring each independently selected from hydroxy, halo, carboxy, (C_1-C_7)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, (C_1-C_7)alkyl, (C_2-C_7)alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_4)alkyl, (C_3-C_7)cycloalkyl(C_1-C_4)alkanoyl, formyl, (C_1-C_8)alkanoyl, (C_1-C_8)alkanoyl(C_1-C_8)alkyl, (C_1-C_4)alkanoylamino, (C_1-C_4)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4)alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulfinyl, (C_1-C_4)alkylsulfonyl and mono-N- or di-N,N-(C_1-C_4)alkylaminosulfinyl, wherein said alkyl and alkoxy substituents in the definition of Ar are optionally substituted on carbon with up to three fluoro; and

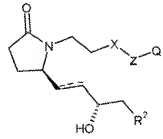
said Ar^1 and Ar^2 moieties are independently optionally substituted on carbon or nitrogen with up to three substituents each independently selected from hydroxy, halo, carboxy, (C_1-C_7)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, (C_1-C_7)alkyl, (C_2-C_7)alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_4)alkyl, (C_3-C_7)cycloalkyl(C_1-C_4)alkanoyl, formyl, (C_1-C_8)alkanoyl, (C_1-C_8)alkanoyl(C_1-C_8)alkyl, (C_1-C_4)alkanoylamino, (C_1-C_4)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4)alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulfinyl, (C_1-C_4)alkylsulfonyl and mono-N- or di-N,N-(C_1-C_4)alkylaminosulfinyl, wherein said alkyl and alkoxy substituents in the definition of Ar^1 and Ar^2 are optionally substituted on carbon with up to three fluoro;

provided that (a) when X is (CH_2)- and Z is -(CH_2)$_3$-, then R^2 is not thienyl, phenyl or phenyl monosubstituted with chloro, fluoro, phenyl, methoxy, trifluoromethyl or (C_1-C_4)alkyl; and (b) when X is (CH_2)-, Z is -(CH_2)$_3$-, and Q is carboxyl or (C_1-C_4)alkoxycarbonyl, then R^2 is not (i) (C_3-C_7)cycloalkyl or (ii) phenyl, thienyl or furyl each of which may be optionally monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from halogen atoms, alkyl

groups having 1 - 3 carbon atoms which may be substituted by one or more halogen atoms, and alkoxy groups having 1 - 4 carbon atoms; and

wherein the second compound is an estrogen, or a pharmaceutically acceptable salt thereof.

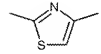
2. The method of claim 1 wherein the first compound is of the formula Ia



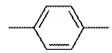
Ia

a prodrug thereof, a pharmaceutically acceptable salt of said compound or said prodrug or a stereoisomer or diastereomeric mixture of said compound, prodrug or salt, wherein:

X is $-CH_2-$; Z is $-(CH_2)_3-$,



or



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and R^2 is Ar wherein said Ar moiety is optionally substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, or on one or both rings if the moiety is bicyclic, with up to three substituents per ring each independently selected from hydroxy, halo, carboxy, (C_1-C_7)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, (C_1-C_7)alkyl, (C_2-C_7)alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_4)alkyl, (C_3-C_7)cycloalkyl(C_1-C_4)alkanoyl, formyl, (C_1-C_8)alkanoyl, (C_1-C_6)alkanoyl(C_1-C_6)alkyl, (C_1-C_4)alkanoylamino, (C_1-C_4)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4)alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_8)alkylthio, (C_1-C_8)alkylsulfinyl,

(C_1-C_4)alkylsulfonyl and mono-N- or di-N,N-(C_1-C_4)alkylaminosulfinyl, wherein said alkyl and alkoxy substituents in the definition of Ar^1 and Ar^2 are optionally substituted on carbon with up to three fluoro.

3. The method of claim 2 wherein the first compound is of formula Ia, a prodrug thereof, a pharmaceutically acceptable salt of said compound or said prodrug or a stereoisomer or diastereomeric mixture of said compound, prodrug or salt, wherein Ar is cyclohexyl, 1,3-benzodioxolyl, thienyl, naphthyl or phenyl optionally substituted with one or two (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, chloro, fluoro, trifluoromethyl or cyano, wherein said alkyl and alkoxy substituents in the definition of Ar are optionally substituted with up to three fluoro.

4. The method of claim 3 wherein the first compound is of formula Ia, a prodrug thereof, a pharmaceutically acceptable salt of said compound or said prodrug or a stereoisomer or diastereomeric mixture of said compound, prodrug or salt, wherein the dotted line is no bond; Q is carboxy or (C_1-C_4)alkoxylcarbonyl; and Z is

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5. The method of claim 4 wherein the first compound is of formula Ia, a prodrug thereof, a pharmaceutically acceptable salt of said compound or said prodrug or a stereoisomer or diastereomeric mixture of said compound, prodrug or salt, wherein Q is carboxy and Ar is phenyl optionally substituted with one (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, chloro, fluoro, trifluoromethyl or cyano, wherein said alkyl and alkoxy substituents in the definition of Ar are optionally substituted with up to three fluoro.

6. The method of claim 5 wherein the first compound is of formula Ia, a prodrug thereof, a pharmaceutically acceptable salt of said compound or said prodrug or a stereoisomer or diastereomeric mixture of said compound, prodrug or salt, wherein Ar is m-trifluoromethylphenyl, m-chlorophenyl or m-trifluoromethoxyphenyl.

7. The method of the claim 6 wherein the first compound is 5-(3-(2S-(3R-hydroxy-4-(3-trifluoromethyl-phenyl)-butyl)-5-oxo-pyrrolidin-1-yl)-propyl)-thiophene-2-carboxylic acid; 5-(3-(2S-(3R-hydroxy-4-(3-trifluoromethoxy-phenyl)-butyl)-5-oxo-pyrrolidin-1-yl)-propyl)-thiophene-2-carboxylic acid or 5-(3-(2S-(4-(3-chloro-phenyl)-3R-hydroxy-butyl)-5-oxo-pyrrolidin-1-yl)-propyl)-thiophene-2-carboxylic acid, or a pharmaceutically acceptable salt thereof.

8. The method of claim 7 wherein the first compound is 5-(3-{2S-[3R-hydroxy-4-(3-trifluoromethyl-phenyl)-butyl]-5-oxo-pyrrolidin-1-yl}-propyl)-thiophene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

9. The method of claim 8 wherein the second compound is 17β-estradiol.

10. The method of claim 8 wherein the second compound is conjugated estrogens.

11. The method of claim 1 wherein osteoporosis, osteoporotic fracture, osteotomy, childhood idiopathic bone loss or periodontitis is treated or wherein bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction is enhanced, vertebral synostosis is induced, long bone extension is enhanced, the healing rate of a bone graft or a long bone fracture is enhanced or prosthetic ingrowth is enhanced.

12. A method of treating osteoporosis, osteoporotic fracture, osteotomy, childhood idiopathic bone loss or periodontitis or enhancing bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction, inducing vertebral synostosis, enhancing long bone extension, enhancing the healing rate of a bone graft or a long bone fracture or enhancing prosthetic ingrowth in a patient in a patient in need thereof, the method comprising continuously administering to the patient in need thereof of a synergistically effective combination of a first compound and a second compound, the first compound being 5-(3-{2S-[3R-hydroxy-4-(3-trifluoromethyl-phenyl)-butyl]-5-oxo-pyrrolidin-1-yl}-propyl)-thiophene-2-carboxylic acid or a pharmaceutically acceptable salt thereof, and the second compound being 17β-estradiol.

13. The method of claim 12 wherein the 5-(3-{2S-[3R-hydroxy-4-(3-trifluoromethyl-phenyl)-butyl]-5-oxo-pyrrolidin-1-yl}-propyl)-thiophene-2-carboxylic acid or a pharmaceutically acceptable salt thereof is continuously administered at a dosage of approximately 0.3 mg/kg/day and the 17β-estradiol is continuously administered at a dosage of approximately 0.01 mg/kg/day.

14. The method of claim 13 wherein the 5-(3-{2S-[3R-Hydroxy-4-(3-trifluoromethyl-phenyl)-butyl]-5-oxo-pyrrolidin-1-yl}-propyl)-thiophene-2-carboxylic acid or a pharmaceutically acceptable salt thereof and 17β-estradiol are continuously administered for a period of at least 28 days.